Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

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Session 3

1. Topic and Author

Experiences from large databases: Are there gender differences?

Viola Vaccarino, MD, PhD

2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Epidemiological and clinical studies have uncovered a puzzling paradox in the epidemiology of ischemic heart disease (IHD) in women. On one hand, women are protected against the development of coronary atherosclerosis compared with men as shown by the fact that women develop IHD later in life, are more likely to develop unstable angina rather than acute myocardial infarction (MI) as the initial manifestation of IHD, and once they develop IHD, they have less extensive coronary artery narrowing compared with men. On the other hand, however, when women develop a MI, they appear to lose this protection. Despite having less severe coronary atherosclerosis, women hospitalized with MI are more acutely ill and have higher complication and mortality rates. These paradoxical facts have stimulated intense research on heart disease in women in the past 10-15 years.

Data from large databases, such as NRMI, have highlighted that women hospitalized with acute MI, compared with men, are older, have more comorbid conditions, are less likely to have chest pain or ST-segment elevations, and are less likely to receive recommended treatments for MI. A major advantage of NRMI versus other databases of MI patients is its large size coupled with its inclusion of patients of all ages, an important difference with respect, for example, to large Medicare databases which have also been used extensively in this area of research. Using NRMI data, therefore, we were able to evaluate in detail presentation characteristics and outcomes in different gender and age subgroups. From this work, it has become clear that younger women (<70 years) with IHD represent the group in which gender differences in presentation and outcome are most marked (1). These findings, which confirmed and expanded preliminary observations (2), were subsequently replicated by other studies (3, 4).

What NRMI data have clearly indicated is that the younger the MI patients, the larger the gender differences in presentation and outcome, whereas usually no differences are found between older men and women (1). Younger women, for example, are more likely than men to have a history of diabetes, CHF and stroke and to have evidence of left ventricular dysfunction on admission. These differences are most marked in women younger than 60 years and decline with age to the point that no differences are noted at older ages (1). Similarly, younger women are less likely than men to present with chest pain or ST-segment abnormalities and to be given an initial diagnosis of MI or unstable angina. Again, differences decline with age and are not noted in older patients. Lastly, younger women have higher rates of in-hospital complications and mortality than men. In the age group <50 years, for example, women have more than two-fold higher mortality rate compared with men. In the age group between 50 and 59, the mortality rate in women is about 70% higher. These differences decline with age and are no longer observed in older patients (70 years or older). For each 10-year decrement in age, the mortality rate for women increases 22% relative to men. These mortality differences are only partially explained by differences in comorbidity, presentation characteristics and treatments between younger women and men. Additional work from our group has shown that the higher mortality risk of younger women compared with men is not limited to the in-hospital post-MI phase but is also seen after discharge (4). In addition, younger women face remarkably higher risks than men after revascularization procedures (5, 6).

Although primarily a disease affecting elderly women, IHD is not uncommon in younger women. In the NRMI-2

database, for example, 36% of all MI's in women were in women <70, and 16% were in women <60. It should be noted that 10% of all deaths in women younger than 65 years have IHD as the underlying cause, a proportion that is higher than for breast cancer.

3. Current challenges and the most important issues for future research

Epidemiological studies and studies from large databases have identified a number of important issues that need to be considered in future research on gender differences in presentation, diagnosis, treatment and outcome of IHD. The first is that because women, on average, develop IHD later in life than men, all differences should be corrected for age. In other words, when presenting gender differences in any of these aspects, we should make sure that we are dealing with gender effects and not age effects. The second issue is that premature IHD in women, i.e., IHD in young or middle-aged women (before approximately age 70), deserves special attention. Different sources of data (epidemiological, pathological, physiological and clinical) suggest that women with IHD are a mixed group, and that younger women represent a high-risk group with distinct risk factors and pathophysiology. Therefore, studies of IHD in women should make an effort to include younger women in addition to older women, and if sample sizes are large enough, results should be examined separately in younger and older patients. The third and perhaps most challenging issue is the need to uncover the reasons for the presentation and outcome differences between men and women with IHD. In the NRMI-2 data, as well as in other large databases, the outcome differences between younger women and men were only partially explained by differences in pre-existing illness and severity characteristics on admission. Interestingly, although younger women were distinctly less likely than men to receive established treatments for MI, such as immediate reperfusion, aspirin and beta-blockers, these treatment differences explained little of the gender differences in mortality (1), a fact that has been shown in other studies (7, 8).

A potential explanation for the differences in presentation and outcome between women (particularly younger women) and men with IHD is a possible ascertainment bias. Because IHD in younger women is relatively uncommon, and because diagnostic tests may be less accurate in this group, only the most severe cases may be diagnosed and treated. Another possible bias is a referral bias, if women with suspected or confirmed IHD are referred for evaluation or treatment later or when they are more severely affected compared with men. Although several studies have pointed out treatment differences between women and men with IHD, the presence of a true bias has been debated, especially regarding the use of revascularization procedures, because optimal care is difficult to establish (for example, determine whether the finding reflects undertreatment of women or rather overtreatment of men) and because patient preferences have rarely been taken into account.

One aspect in the current literature that argues against a referral bias, but that opens up wider issues of pathophysiology and management, is the fact that women with established IHD have less extensive, rather than more extensive, coronary artery narrowing compared with men. This has been a consistent finding in different series of patients, including patients hospitalized with MI (9, 10), patients who die suddenly of coronary causes (11), patients who survive a cardiac arrest (12), and patients referred for revascularization procedures (5, 13, 14), despite the fact that women were older, more symptomatic and more critically ill at presentation. These findings raise two crucial questions that need to be addressed: 1) Is the pathophysiology of IHD in premenopausal or middle-aged women different from the more common disease of older women and of men, i.e., does it involve pathways other than extensive coronary narrowing? Possible unique pathophysiological pathways could involve, for example, clotting abnormalities, hypercoagulable states, coronary spasm, or diffuse microvascular disease. 2) Are the traditional diagnostic tests for coronary heart disease, such as coronary angiography, inadequate to evaluate coronary risk in young and middle-aged women? If the pathophysiology involves pathways other than coronary stenosis, there might be considerable under-diagnosis of IHD in women using traditional methods particularly in the early phase of the disease, i.e., when women are young or middle-aged. While the reasons behind gender-related referral patterns need clarification, research should focus on devising new ways to diagnose IHD accurately in women early in the disease process.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

A current challenge is the lack of awareness of women of their risk of heart disease, especially young and middle-aged women. Some of the differences in presentation and outcomes observed in large databases may reflect poor awareness of cardiac symptoms and cardiac risk among women, resulting in longer delays in

seeking medical attention. Another challenge is the limitations (particularly the high false positive rate) of the available diagnostic tests to identify IHD in women. Because of these diagnostic difficulties and the lower prevalence of IHD in women, these tests are less cost-effective in women, and health care providers may be less aggressive in pursuing a diagnosis of IHD in women at an early stage.

5. Translating new findings to improved diagnosis and treatment/saving lives.

The peculiar characteristics of IHD in women, particularly younger and middle-aged women, have diagnostic implications that affect management decisions and, therefore, prognosis. Some of the presentation differences between men and women with IHD observed in large databases may reflect characteristics of pathophysiology and early manifestations of IHD that are unique to women. If the early symptoms, signs, and pathophysiology of IHD in women differ from those of men, which are considered "traditional," the condition may be more difficult to recognize in women at an early stage with the tools we have in hand. Therefore, by devising new diagnostic modalities capable of recognizing IHD early in the disease process in women in a cost-effective way, or by discovering new risk factors or prognostic factors, perhaps unique to women, we should be given the opportunity of beginning preventive strategies early enough to prevent or delay the development of IHD in women and improve the prognosis of women who already have established IHD.

6. References.

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